



King's Research Portal

DOI:

[10.1016/j.schres.2016.01.024](https://doi.org/10.1016/j.schres.2016.01.024)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Lally, J., Tully, J., Robertson, D., Stubbs, B., Gaughran, F., & MacCabe, J. H. (2016). Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: A systematic review and meta-analysis. *Schizophrenia Research*, 171(1-3), 215-224. <https://doi.org/10.1016/j.schres.2016.01.024>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: A
systematic review and meta-analysis

Authors:

John Lally, John Tully, Dene Robertson, Brendon Stubbs, F Gaughran* J H MacCabe*

*Authors contributed equally and should be acknowledged as joint senior authors

Dr John Lally, MB MSc MRCPsych, Clinical Research Fellow,

Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience (IoPPN),

King's College London, London, United Kingdom and National Psychosis Service, South London and

Maudsley NHS Foundation Trust, London, United Kingdom.

Dr John Tully MB MRCPsych

NIHR Academic Clinical Fellow and Specialist Registrar in Forensic Psychiatry, Department of Forensic

and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience

Dr Dene Robertson MRCPsych,

Consultant Psychiatrist in Behavioural and Developmental Psychiatry, Clinical Academic Group with South London and Maudsley (SLaM) NHS Foundation Trust and Honorary Senior Lecturer Institute of Psychiatry, Psychology & Neuroscience (IoPPN) King's College London.

Brendon Stubbs, MSc, MCSP, PhD

Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, and Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, United Kingdom

Dr Fiona Gaughran MB, BCh, BAO, FRCPI, FRCP, FRCPsych, MD,

Lead Consultant Psychiatrist, National Psychosis Service, South London and Maudsley NHS Foundation Trust, Senior Lecturer, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, United Kingdom.

Dr James H MacCabe BSc MBBS FRCPsych MSc PhD

Reader in the Epidemiology of Psychosis, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London and Honorary Consultant Psychiatrist,

National Psychosis Service, South London and Maudsley NHS Foundation Trust, London, United Kingdom

Corresponding author: Dr John Lally, MB MSc MRCPsych

Clinical Research Fellow,

PO63, Department of Psychosis Studies

Institute of Psychiatry, Psychology & Neuroscience (IoPPN),

King's College London,

De Crespigny Park

London SE5 8AF

Email: john.lally@kcl.ac.uk

Tel: (0044) (0)20 7848 0216

Fax:(0044) 020 7848 0287

Word count-

Abstract: 273

Article: 5200

Total Word count: 5473

Abstract

The primary aim of this systematic review and meta-analysis was to assess the proportion of patients with Treatment Resistant Schizophrenia (TRS) respond to ECT augmentation of clozapine (C+ECT). We searched major electronic databases from 1980 to July 2015. We conducted a random effects meta-analysis reporting the proportion of responders to C+ECT in RCTs and open-label trials. Five clinical trials met our eligibility criteria, allowing us to pool data from 71 people with TRS who underwent C+ ECT across 4 open label trials (n=32) and 1 RCT (n=39). The overall pooled proportion of response to C+ECT was 54%, (95% CI: 21.8-83.6%) with some heterogeneity evident ($I^2=69\%$). With data from retrospective chart reviews, case series and case reports, 192 people treated with C+ECT were included. All studies together demonstrated an overall response to C+ECT of 66% (95% CI: 57.5-74.3%) (83 out of 126 patients responded to C+ECT). The mean number of ECT treatments used to augment clozapine was 11.3. 32% of cases (20 out of 62 patients) with follow up data (range of follow up: 3-468 weeks) relapsed following cessation of ECT. Adverse events were reported in 14% of identified cases (24 out of 166 patients). There is a paucity of controlled studies in the literature, with

only one single blinded randomised controlled study located, and the predominance of open label trials used in the meta-analysis is a limitation. The data suggests that ECT may be an effective and safe clozapine augmentation strategy in TRS. A higher number of ECT treatments may be required than is standard for other clinical indications. Further research is needed before ECT can be included in standard TRS treatment algorithms.

Keywords: Treatment resistant schizophrenia; clozapine; ECT; psychosis; schizoaffective disorder

Conflict of Interest

Dr Gaughran has received honoraria for advisory work and lectures from Roche, BMS, Lundbeck, and Sunovion and has a family member with professional links to Lilly and GSK;

The other authors declare no conflict of interest.

Acknowledgement

Dr Lally and Dr MacCabe are both supported by CRESTAR (CRESTAR project, <http://www.crestar-project.eu/>) EU-FP7 grant number 279227; Dr MacCabe is also supported by MRC grant nos. MR/L011794/, MR/L003988/1 and MC_PC_13065) and by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology and Neuroscience, Kings College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

The authors would like to thank Dr. Rohit Garg, M.D., Senior Research Associate, Department of Psychiatry, Government Medical College & Hospital, Chandigarh. India, 160036; Dr Tomasz Pawelczyk, MD, PhD, Department of Affective and Psychotic Disorders, Medical University of Lodz, Poland; Dr Itziar Flamarique MD, PhD, Child and adolescent psychiatrist, Clinical research fellow,

Hospital Clínic of Barcelona for providing unpublished data to complete the systematic review; Dr Sandeep Grover Associate Professor, Department of Psychiatry, PGIMER, Chandigarh -160012, INDIA; Dr Diana Kristensen MD, Psychiatric Centre Copenhagen, Copenhagen, Denmark and Professor TANG Wai Kwong, Department of Psychiatry, The Chinese University of Hong Kong, Hong Kong for clarifying the methodology of their studies.

Title: Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: A systematic review and meta-analysis

Introduction

Schizophrenia is a chronic disabling illness, with a lifetime prevalence rate of 0.6-1% (Saha et al., 2005). Approximately 30% of people with schizophrenia do not respond to conventional antipsychotic therapy (i.e. first or second generation antipsychotics (FGAs or SGAs) and meet the criteria for treatment resistant schizophrenia (TRS) (Brenner et al., 1990; Conley and Buchanan, 1997; Meltzer, 1997).

Clozapine remains the only effective medication for TRS, and is the only licensed treatment. However, 30-40% of TRS patients fail to respond to clozapine (Meltzer, 1992). Those unresponsive to clozapine, are the most disabled of all patients with schizophrenia, with illnesses characterised by persistent

symptoms, a poorer quality of life, increased disability and a greater economic cost than treatment responsive patients (Kennedy et al., 2014). Numerous pharmacological strategies have been explored, including the addition of a second antipsychotic, mood stabilisers, anxiolytics, antidepressants, anti-inflammatories and glutamatergic agents, but with no robust replicated evidence to support the efficacy of any of these strategies (Cipriani et al., 2009; Porcelli et al., 2012; Remington et al., 2005; Taylor et al., 2012; Tranulis et al., 2006).

The use of ECT in schizophrenia is supported by findings from a Cochrane review indicating that treatment with ECT is significantly more likely to result in clinical improvement than placebo or sham ECT (n=9 trials; n=400 patients), with ECT resulting in fewer relapses and increased rates of hospital discharge than sham ECT (Tharyan and Adams, 2005). However, recommendations for the use of ECT in schizophrenia are inconsistently reflected in current national clinical guidance. For example, the United Kingdom's National Institute of Care Excellence (NICE) does not recommend ECT as a treatment for schizophrenia, unless prominent catatonia exists (NICE, 2014), whilst the American Psychiatric Association (APA) recommends that ECT should be considered when there is treatment resistance (APA, 2008).

There is clear evidence that many users of mental health services hold negative views regarding ECT, although there has been little research on the attitudes of patients with treatment refractory

schizophrenia to ECT (Rose et al., 2003; Rose et al., 2005). Rose et al., found that perceived coercion and a lack of information about ECT and potential adverse effects were highlighted by patients as problems with their ECT treatment (Rose et al., 2005).

A recent RCT of ECT augmentation in clozapine-resistant schizophrenia showed encouraging results (Petrides et al., 2015). This prompted us to conduct an up-to-date systematic and meta-analytic review of the literature, to assess the efficacy of C+ECT in TRS. We conducted a systematic review and meta-analysis to assess the pooled proportion of responders to C+ECT in people with TRS. Further, we sought to identify studies that have assessed the use of maintenance ECT in patients taking clozapine. We reported data on the safety and adverse effects of augmentation of clozapine with ECT, as well as patients' perspectives of ECT, when any of these were reported in the identified studies. However, we did not systematically search for studies reporting these aspects.

Methods

We performed a literature search to identify all published case series/case reports, and all observational and interventional studies, both RCTs and open label studies up until January 2015, investigating or describing ECT as a clozapine augmentation strategy in treatment resistant schizophrenia (TRS) and/or schizoaffective disorder. This systematic review was conducted in

accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standard (Moher et al., 2009).

Inclusion criteria

Studies were included in this systematic review if they: (1) included adult participants (>18 years, with no upper age limit) with a diagnosis of treatment resistant schizophrenia or schizoaffective disorder and (2) reported studies where ECT was used to augment clozapine treatment and (3) had been written in English and published in a peer reviewed journal since 1980. We included both controlled and non-controlled studies (including open label trials), as well as retrospective chart reviews or case series/case reports.

Exclusion criteria

We excluded (1) articles relating to ECT as a clozapine augmentation strategy for bipolar affective disorder, mania or psychotic depression, (2) studies in which clozapine was added after ECT had been commenced and/or (3) in which clozapine and ECT were not used concurrently.

Information sources and searches

Two independent reviewers (JL, JT) performed an electronic search using Medline, Embase, PsychInfo, Cochrane Schizophrenia Group, and Google Scholar from January 1980 until July 2015. The following basic search terms were used, both alone and in combinations: “schizophrenia,”

“clozapine,” “resistant,” “refractory,” and “electroconvulsive therapy,” “ECT”. In addition, the reference lists of the retrieved articles and relevant review articles were examined for cross-references. When necessary, corresponding authors were contacted to clarify study eligibility and/or acquire additional data.

Study selection and exclusion

All applicable abstracts were obtained, and independently examined by two of the authors (JL & JT). The two appraisers applied the eligibility criteria and a list of full text articles was developed through consensus. There was no search for unpublished works, although authors were contacted for clarification where necessary. This selection process refined the number of relevant articles to 29 clinical reports. Two of the publications were controlled studies, and we further identified 4 open label studies, 2 retrospective chart reviews, 6 case series and 15 case reports. We distinguished the data from controlled versus non-controlled (uncontrolled) studies to achieve a workable summary of our findings.

Primary outcome

The primary outcome was the response rate to C+ECT in people with TRS and if available, to C+Sham ECT or no ECT. We used dichotomous data of clinical improvement, as defined by the individual

studies, as the primary outcome measure of efficacy. These included response rates to treatment as measured by a pre-defined reduction in total BPRS, PANSS or CGI scores.

Data extraction

Articles included were critically reviewed by two authors (JL and JT) and the following information extracted where possible: demographic and clinical characteristics of patients, dosage and duration of clozapine monotherapy (before ECT), plasma clozapine levels reported pre- and post-ECT, mean clozapine dosage during ECT, number of ECT sessions, application of electrodes (unilateral or bilateral), mean ECT stimulus dosage received, clinical outcome, outcome measures used, adverse effects reported, information on patients' perspectives, duration of follow-up, use of maintenance ECT and pattern of maintenance ECT use, other medications concurrently used during the combined treatment or during follow-up, and relapses reported during follow-up.

Meta-Analysis

All extracted data from the studies included were entered into Comprehensive Meta-Analysis version 2.0 (CMA v2, Englewood, NJ, USA).

We defined our primary outcome, response to C+ECT, according to the included study investigators' operational definitions of response as provided in the original reports. Where binary outcomes were

used, we calculated the pooled proportion of those that responded with clinical improvement across all included studies together with 95% confidence intervals (CI)

Due to the methodological variability in the included studies, we anticipated heterogeneity and a random effects meta-analysis was employed. We quantified any observed heterogeneity by computing the I^2 statistic (Higgins et al., 2003).

We assessed publication bias with a visual inspection of funnel plots and quantitative testing through the use of Begg–Mazumdar (Begg and Mazumdar, 1994) and Egger bias tests (Egger et al., 1997).

Results

Study selection, study and participant characteristics

The study selection process, search results, and reasons for exclusion are given in figure 1.

The initial search yielded 1148 references. After checking titles and abstracts, 56 full texts were screened and 29 of these were included for data extraction. Citations within a paper were included as an additional source of references. At the full text review stage we contacted 5 author groups and 3 provided additional data to enable inclusion (Garg R et al., 2012; Grover et al., 2015; Pawełczyk et al., 2014).

Meta-Analysis

It was possible to pool data on the proportion of responders across 71 trial participants who underwent ECT across 5 studies, which included 4 open label trials (n=32) and 1 RCT (n=39). Overall, the proportion of people that responded to treatment was 54% (95% CI 21.8- 83.6%) (figure 2). There was evidence of some heterogeneity ($I^2=69\%$). A subgroup analysis demonstrated that the proportion of those that responded was 56% (95% CI: 19.4-87.2%) in 4 open label studies and 48.7% (95%CI: 33.6-64.0%) in the RCT.

The funnel plot was broadly symmetrical (figure 3), and the Begg–Mazumdar (Kendall's tau=-0.11, $P=.80$) and Egger bias tests (intercept =0.98, $p=0.26$) did not indicate any publication bias.

We were unable to use data from the second identified RCT in the meta-analysis, as this study did not report a clinical response using dichotomised data of clinical improvement(Masoudzadeh and Khalilian, 2007). Only one of the two controlled studies(Petrides et al., 2015) reported response rates in the treatment versus control groups, thus precluding a meta-analysis of comparisons between treatment groups and control groups.

Included studies

Table 1 gives an overview of included controlled (n=2) and open label trials (n=4) and retrospective chart reviews (n=2). Supplementary Table 1 gives an overview of case series included (n=6) (Benatov et al., 1996; Cardwell and Nakai, 1995; Frankenburg et al., 1993; Grover et al., 2015; Kales et al., 1999;

Kurian et al., 2005). Supplementary Table 2 provides an overview of included case reports (n=15) (Bannour et al., 2014; Bhatia et al., 1998; Biedermann et al., 2011; Gerretsen et al., 2011; Husni M, 1999; Keller et al., 2009; Klapheke, 1991; Lee et al., 2008; Manjunatha et al., 2011; Safferman and Munne, 1992; Sienaert et al., 2004; Sinha and Shah, 2013; Vowels et al., 2014; Yoshino et al., 2014) (Manjunatha *et al.*, reported on two individual case reports). Overall, these studies and reports include a total of 192 patients with a diagnosis of treatment resistant schizophrenia or schizoaffective disorder treated with C+ECT.

Controlled trials

We identified two controlled trials. The study of Petrides et al., (Petrides et al., 2015), used a single blind randomised crossover design to compare clozapine use only (n=19) versus clozapine augmented with ECT (n=20) in patients with TRS. In this study 50% of the C+ECT group achieved treatment response (defined by a > 40% reduction in BPRS scores) by the end of 8 weeks compared with none of those in the clozapine-only group ($F=5.38$, $df=8, 238$, $p<0.0001$). During a subsequent crossover phase (unblinded), members of the clozapine-only arm who had failed to respond (which transpired to be all of them) were treated with C+ECT. 48% obtained a treatment response when ECT was added. A total of 19 of the 39 participants (48.7%) had at least a 40% reduction in psychotic symptoms after receiving C+ECT. There was no significant difference between pre- and post-treatment global neurocognition

scores between the two treatment groups. Further, no significant differences were found between the groups in the executive functioning and episodic memory domains. However, reduced processing speed was associated with ECT administration (with a mean decrease in the Rey Auditory Verbal Learning Test score of 1.5 (0.5) in the C+ECT group compared to the clozapine-only group ($p=0.0063$) when measured within 1 week of the final 8-week ECT course). Two people in the C+ECT group each had ECT treatment delayed by one day on one occasion, due to confusion.

A second controlled study by Masoudzadeh et al., (total $n=18$) compared ECT alone ($n=6$), clozapine alone ($n=6$) and C+ECT ($n=6$) (Masoudzadeh and Khalilian, 2007). However, it should be noted that the two studies differed in their inclusion criteria: in the Petrides et al., study, the main inclusion criterion was resistance to clozapine, whereas in Masoudzadeh et al., the main inclusion criterion was resistance to non-clozapine antipsychotics. Masoudzadeh et al., did not provide a response definition; therefore response rates were not reported. Instead, mean changes in PANNS scores were given. Compared to the pre-treatment baseline there was a significant decrease of 71% (from 99-29) in PANSS total scores in the C+ECT group, compared to a 40% decrease (from 99-60) with ECT treatment alone, and a 46% decrease (from 96-52) with clozapine monotherapy ($F=189.15$, $df=4,63$, $p<0.0001$) (Masoudzadeh and Khalilian, 2007). In addition, compared to pre-treatment baseline, patients treated with C+ECT had an 80% (from 26 to 5) decrease in mean PANSS positive symptom

subscale scores compared to the other groups ($p < 0.001$). In the ECT alone group there was a mean decrease in positive symptoms of 51 % (from 25 to 12); whilst in patients taking clozapine alone the mean decrease was 31% (from 23 to 16). The C+ECT group had a 60% decrease in mean PANSS negative symptom subscale score (from 33-13), with the clozapine monotherapy group having a 63% decrease (from 32-12). The ECT alone group had a 29% decrease (from 31-22), though the differences between the groups were not statistically significant. This study reported no serious adverse events in the C+ECT group, with no difference between Mini Mental State examination (MMSE) scores between the start and end of the study between the different treatment groups.

Taken together these two controlled studies administered a mean of 15.1 ECT treatments per patient by pre-defined protocols. All patients had a diagnosis of TRS, but those in the Petrides et al., trial were additionally resistant to clozapine (Petrides et al., 2015). Participants in the Petrides et al study were treated with bilateral (BL) ECT and those in the Masoudzadeh et al., 2007 treated with unilateral (UL) ECT (Masoudzadeh and Khalilian, 2007).

Prospective open-label trials

Four prospective open-label studies were found in the literature search (see table 1), with a total of 32 patients identified. The majority of patients ($n=24$ out of 32) were treated with BL ECT and the mean number of ECT treatments was 11.6. None of the open label studies used a predetermined number of

ECT treatments. 73% responded to ECT augmentation of clozapine in one open label trial (Kho et al., 2004). In another study 8 out of 11 patients showed significant improvements in BPRS scores (response defined as a BPRS decrease $> 30\%$; with one patient showing a non-significant improvement in BPRS scores (an 8.2% decrease in BPRS scores) and $n=2$ patients showing no improvement) (Garg R et al., 2012). Only 25% of patients showed significant improvement in PANSS total scores in another open label trial, though 50% had a significant reduction in PANSS positive subscale scores (Pawelczyk et al., 2014). In a smaller study, two patients showed a significant improvement in clinical global impression (CGI) scores (Hustig and Onilov, 2009).

No adverse events were reported in two of the open label trials ($n=13$ patients in total (Garg R et al., 2012; Hustig and Onilov, 2009)). In one of the studies, prolonged seizures (≥ 90 s) were observed in 3 patients (90, 100, and 200 seconds) (Pawelczyk et al., 2014). In the other open label study, two patients reported memory problems (not quantified), with one experiencing confusion following every ECT treatment. This patient was treated with clozapine 450 mg, lithium carbonate 1000mg and oxazepam 50mg concurrent to ECT (Kho et al., 2004). No other adverse events were reported.

Follow up data were provided in two of the trials ($n=10$ patients) (Hustig and Onilov, 2009; Kho et al., 2004), with 50% ($n=5$) of patients in total relapsing (all in Kho et al., 2004 (Kho et al., 2004)) over a mean follow-up period of 16 weeks (range=4–52 weeks).

Retrospective chart reviews

Two retrospective chart reviews were identified, with a total of 63 patients included (Gazdag et al., 2006; Kristensen et al., 2011). All patients were treated with twice weekly BL ECT for a mean of 7.4 ECT treatments. . In one of the studies, 18 out of 20 patients were recorded as having an 'excellent or good response to ECT augmentation', but with 7 out of 20 requiring maintenance ECT therapy, due to relapses following the initial ECT treatment (Kristensen et al., 2011). In the other retrospective study (n=43) the mean improvement in CGI score was 2.3(Gazdag et al., 2006). This improvement was most marked in the schizoaffective disorder subgroup (n=16), where a mean decrease in CGI of 6.25 to 2.30 was recorded, compared to a mean decrease in CGI of 5.86 to 4.65 in those with a diagnosis of schizophrenia (n=26, hebephrenic and catatonic subtypes). Transient side effects of headache (n=2), confusion (n=2) and raised systolic blood pressure (n=2) were reported (Gazdag et al., 2006).

Quality of life

We identified one secondary analysis of an open label study which quantitatively assessed quality of life (QoL)scores (using the World Health Organization Quality of Life Scale) of those with TRS treated with C+ECT (n=11). This found significant improvement in three of out of four QoL domains: satisfaction with physical capacity, health and environment (Garg R et al., 2012; Garg et al., 2011).

Case series and case reports

The identified case series and case reports are described in supplementary tables 1 and 2. Fifty two patients were identified in total in the case series and case reports, and all, except one (Biedermann et al., 2011), were treated with BL ECT. The mean number of ECT treatments was 12.8, with a clinical response rate of 76% (n=28/37 patients with clinical response quantified). The mean dose of clozapine used concurrent to ECT was 588.5 mg daily (for a total n=26 patients with dose documented). One patient died of a pulmonary embolism following ECT; the role of ECT in this was unclear

Results summary for all 192 patients, including case series and case reports

Taken together, the included studies and case reports, showed an overall response to clozapine augmented with ECT of 76% (83 out of 126 patients responded to C+ECT). The mean number of ECT treatments used for all included studies and case reports (for n=192 patients) was 11.3 (range 4-30). The mean number of ECT treatments used in the controlled (n=2) and open label trials (n=4) was 13.0 (for total n=77). The mean clozapine dose used was 412.3 mg daily (for n=127 patients), with a mean serum clozapine level of 772.6ng/ml (recorded for n=52 patients treated with an average clozapine dose of 506.9 mg daily (Gerretsen et al., 2011; Keller et al., 2009; Kho et al., 2004; Petrides et al., 2015)). In those non-controlled studies, case series and case reports with follow up data, a relapse rate

of 32% (20 out of 62 patients), was identified following an initial response to clozapine augmentation with ECT. Adverse events were reported in 14% of identified cases (24 out of 166 patients) (n=1 death secondary to pulmonary embolism; n=6 with post-ictal confusion; n=5 with prolonged seizure; n=4 with transient memory problems; n=3 with delirium; n=1 with aspiration pneumonia; n=2 tachycardia; n=1 with high blood pressure; n= 1 truncal dystonia ('Pisa syndrome')).

Discussion

We present the first systematic review and meta-analysis of C+ECT in TRS, demonstrating a pooled estimate response of 54% to C+ECT. This systematic review is the most comprehensive study to date, incorporating newly available data and collating the available literature regarding the response to clozapine augmented with ECT (C+ECT) in TRS.

We identified two randomised controlled trials both of which both demonstrated favorable results for C+ECT, when compared to ECT or clozapine monotherapy (Masoudzadeh and Khalilian, 2007; Petrides et al., 2015). These results are from the best conducted trials in this area so far; however the literature in this area is sparse and the methodological designs not as robust as for most pharmaceutical trials, owing to the difficulty of blinding. The two controlled trials were very different in the robustness of design and in the clinical relevance of their study findings. The Petrides et al.,(2015)

trial addressed the important clinical question of whether ECT is a useful next step after clozapine non-response in a treatment sequence, providing evidence that it is an effective augmentation strategy (Petrides et al., 2015). The smaller trial from Masoudzadeh et al., (2007) suggests that C+ECT is better than either ECT or clozapine alone in TRS. However, this study was limited by a small sample size, lack of data in relation to mean clozapine doses, dose changes during the study, and unknown serum clozapine levels within the different groups (Masoudzadeh and Khalilian, 2007). The direct clinical relevance of this study is therefore uncertain. The findings from controlled trials are supported by generally positive outcomes for C+ECT in open label trials, retrospective chart reviews, case series and the majority of case reports.

Our findings are broadly in line with earlier reviews that indicated that C+ECT was an efficacious and safe treatment for clozapine refractory psychosis (Havaki-Kontaxaki et al., 2006; Kupchik et al., 2000)).

Our systematic review includes many more cases where C+ECT was employed as a treatment strategy, and this along with other findings are compared in Table 2 with the two previous systematic reviews of C+ECT (Havaki-Kontaxaki et al., 2006; Kupchik et al., 2000).

Limitations of this review

Limited primary data

There is a paucity of controlled studies in the literature, with only one single blinded randomised controlled study located (Petrides et al., 2015), and the findings of that study are limited by the numbers recruited and the lack of a sham control group. The overreliance on open label studies in the meta-analysis may have led to an overestimation of the identified response rate to C+ECT.

Heterogeneity of response definitions

Owing to the heterogeneity of response definitions, it was necessary to pool data from studies that used different definitions of response. We recognise that this limits the validity of the findings.

Publication bias

We included one RCT and four open label trials with individual participant data in our assessment for publication bias in the meta-analysis. Visually, our funnel plot showed only minor asymmetry and Egger's test for asymmetry was not significant ($P=0.25$). While this shows no evidence of publication bias, it is not possible to exclude given the small number of studies.

Lack of blinding

The absence of any double blinded data on efficacy or adverse effects limits the conclusions that can be drawn. This is of particular concern with ECT given the potentially powerful placebo effect. It is, of course, very difficult to conduct single blind studies of ECT, let alone double blind studies. Sham ECT, where the participant is briefly anaesthetised but receives no ECT, could theoretically allow blinding,

although the post-ictal confusion that often occurs post-ECT may unblind treatment in some cases.

The use of sham ECT in a clinical trial requires careful ethical consideration, given that patients are exposed to the potential risk of anesthesia but without the potential benefits of treatment.

English language and exclusion criteria

We only included studies published in English. The use of ECT in schizophrenia appears to be more common in Asian countries, and clozapine is commonly prescribed in China, but we did not include Chinese databases in the systematic review. However, it is noteworthy, that the Cochrane review on ECT combined with antipsychotics in schizophrenia (Tharyan and Adams, 2005), as well as this review, found substantial numbers of studies and reports from India and Thailand which were reported in English. We were also able to recover important data from open label trials of ECT augmentation of antipsychotics (including clozapine) (Garg R et al., 2012; Pawełczyk et al., 2014), which allowed for additional C+ECT outcomes to be included.

We excluded studies in adolescent and children. This meant that a recent observational study of ECT augmentation of antipsychotic treatment (which included n=6 adolescents with C+ECT) was excluded (Flamarique et al., 2012).

Lack of quality of life and service user perspective

Only one of the identified studies assessed quality of life (Garg et al., 2011). The assessment of patient and carer perception of clozapine augmentation with ECT was not reported in any of the other identified studies or cases. This is an area which requires further study, and we recommend that service-user perspectives are included in all future controlled trials of C+ECT. The views of service users and carers is particularly important, given the ongoing stigma and controversy which surrounds ECT treatment. A well-constructed systematic review of patients' perspectives on ECT, including a qualitative analysis of patient testimony, highlighted that service users perceived coercion and memory problems with ECT treatment in depression (Rose et al., 2003), but this has not been investigated in treatment resistant schizophrenia populations, where the balance of risks and benefits may be different.

Implications for clinical practice

Despite the caveats discussed above, the results suggest that ECT may be an effective augmentation strategy in patients who fail to respond to clozapine monotherapy.

Number and dose of treatment required

A consistent finding across studies is the greater number of ECT treatments used in clozapine augmentation in TRS than the six ECT treatments used on average in depression (Charlson et al., 2012; Waite and Easton, 2013). We identified an average of 15.1 ECT treatments (pre-determined ECT

schedules) in the controlled studies, and 11 ECT treatments in all the included studies and case reports; the vast majority received bilateral ECT (BL-ECT) at a twice weekly frequency.

In the best designed controlled study an average of 16 ECT treatments was used, which achieved a response rate of 50%. (Petrides et al., 2015) However, this was a predetermined schedule aiming for 20 ECT treatments, and which was not based on randomised comparisons of short versus longer courses of treatment.

Taken together, these data suggest, but by no means prove, that a larger number of ECT treatments may be required in order to achieve a response in TRS than is the case in depression.(Charlson et al., 2012)

Adverse effects with C+ECT

There was a low rate of adverse events reported with ECT augmentation, but it is possible that adverse effects may have been under-reported, and only 4 out of 8 studies reported adverse effects in a systematic way. Clozapine lowers the seizure threshold, and it has been suggested that prolonged seizures with ECT therapy may be precipitated by combined ECT-clozapine treatment. (Bloch et al., 1996) Three patients in an open label trial had one individual episode each of prolonged seizure activity with no reported sequelae. (Pawelczyk et al., 2014) From a case series a further two patients were

documented to have developed prolonged seizures after an ECT treatment which required treatment with lorazepam.(Grover et al., 2015) There were no other reports of prolonged seizure activity.

ECT use is often limited due to concerns about cognitive side effects, including memory loss. This was not widely observed in our review. In the best designed controlled trial, there was no significant change in global neurocognition (as measured by Mental State Examination (MMSE) scores) between baseline and end of ECT (Petrides et al., 2014). Additional cognitive impairment tests for executive functioning and episodic memory failed to identify significant differences between the C+ECT and clozapine only groups, though processing speed was impaired in the C+ECT group one week following the treatment course.

Cognitive adverse events as determined by changes in MMSE scores, were not found in the other controlled study.(Masoudzadeh and Khalilian, 2007) There was a low rate of subjective reports of memory problems in the non-controlled studies (n=4/146 patients reported memory problems), although it is not clear to what extent this information was sought by the researchers and to what extent they relied on spontaneous reporting by the patients. There were no reports of significant cardiac arrhythmias, although mild cardiac adverse events of tachycardia (Bhatia et al., 1998; Safferman and Munne, 1992) and raised blood pressure (Safferman and Munne, 1992) were described in case reports.

In one case report, a patient died following a pulmonary embolus.(Sinha and Shah, 2013) He had been treated with an alternate day ECT schedule, though there is no detail given in respect to ECT dose used, seizure duration, and other ECT related side effects, nor is there any information given in relation to the dose of clozapine used at the time. There is no indication whether he was receiving treatment for catatonia or that a DVT was identified. While ECT was not clearly implicated, and it is likely that the death led to the publication of the case report, future studies should assess whether the risks of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) may be increased by treatment with ECT. Clozapine itself has been identified as a potential risk factor for venous thromboembolism, though there has been no systematic assessment of the prevalence of DVT or PEs associated with ECT, with there been only one other case report of fatal PE associated with ECT use. (Kursawe and Schmikaly, 1988) A handful of other case reports of PE occurring in the context of ECT exist, but again do not allow for definitive associations to be made.

Follow-up data on C+ECT

Follow-up data on patient response in the medium to longer term is lacking in the literature. This review noted the well-recognised problem of patients who relapse in the months following discontinuation of ECT. (Kho et al., 2004; Kristensen et al., 2011) We identified a high relapse rate of 32% in the weeks to months after ECT discontinuation, though this finding was limited by the paucity of follow up data.

There are little data to guide practice on discontinuation of ECT. Consideration for a stabilisation period of ECT post remission from C+ECT may be warranted, followed by a gradual reduction in frequency of ECT.

Despite the low rates of cognitive dysfunction reported in the reviewed literature, caveats regarding the need for monitoring for cognitive dysfunction with C+ECT use in practice remain.

Implications for research

We consider that double blind randomised controlled clinical trials are not only possible, but are essential to determine whether these encouraging findings are sustained. The main obstacle to conducting a properly blinded trial is the ethical question as to whether it is justifiable to administer sham ECT as part of a clinical trial, whereby the patient receives an anaesthetic but no treatment. This drawback may be mitigated by using crossover designs, whereby all patients receive the active treatment as well as the sham treatment, provided that participants have a full understanding that they will undergo sham ECT as part of the crossover design. Ratings of response must be blind to treatment arm.

Another barrier, which affects all studies in TRS, particularly those who have not attained a sufficient clinical response to clozapine, is that patients may lack capacity to consent to be recruited into clinical

trials. It may be appropriate in such instances to involve carers or other consultees in the decision as to whether to participate in the trial.

Furthermore it is important that patient and carers are involved in the design and conduct of any study of ECT. We hope that this may lead to research that allows the treatment to be tested with full acknowledgement and investigation of adverse effects, including memory problems, and perceptions of treatment with ECT in TRS both before and after the treatment.

Longer term studies are required to assess the impact of the combination therapy on longer term remission, functional outcomes and adverse effects.

Conclusions

It is clear from this review that the efficacy and adverse effects of a C+ECT in patients with clozapine refractory schizophrenia remains poorly researched, most probably due to the practical challenges in establishing double blind ECT augmentation of clozapine trials in TRS. However a growing body of research from controlled and open trials and from case reports indicates that ECT may be an efficacious and safe clozapine augmentation strategy in TRS.

We can conclude that ECT should not be dismissed as a potential clozapine augmentation strategy in TRS, and that further well controlled ECT trials are required to evaluate the efficacy of the combination both in the short and long term. Further research is needed to determine the place of ECT in TRS

treatment algorithms, including greater evidence on predictors of response, adverse events, the costs and benefits of this treatment and the experiences of service users and carers.

References

- APA, 2008. The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging (A Task Force Report of the American Psychiatric Association). American Psychiatric Publishing.
- Bannour, S., Bouhlel, S., Krir, M.W., Amamou, B., Ben Nasr, S., El Kissi, Y., Ben Hadj Ali, B., 2014. Combination of maintenance electroconvulsive therapy and clozapine in treating a patient with refractory schizophrenia. *J ECT* 30, e29–e30.
- Begg, C.B., Mazumdar, M., 1994. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 50(4), 1088-1101.
- Benatov, R., Sirota, P., Megged, S., 1996. Neuroleptic-resistant schizophrenia treated with clozapine and ECT. *Convuls Ther* 12(2), 117-121.
- Bhatia, S.C., Bhatia, S.K., Gupta, S., 1998. Concurrent administration of clozapine and ECT: a successful therapeutic strategy for a patient with treatment-resistant schizophrenia. *J Ect* 14(4), 280-283.
- Biedermann, F., Pfaffenberger, N., Baumgartner, S., Kemmler, G., Fleischhacker, W.W., Hofer, A., 2011. Combined clozapine and electroconvulsive therapy in clozapine-resistant schizophrenia: clinical and cognitive outcomes. *J ECT* 4, 61-62.
- Bloch, Y., Pollack, M., Mor, I., 1996. Should the administration of ECT during clozapine therapy be contraindicated? *The British Journal of Psychiatry* 169(2), 253-254.
- Brenner, H.D., Dencker, S.J., Goldstein, M.J., Hubbard, J.W., Keegan, D.L., Kruger, G., Kulhanek, F., Liberman, R.P., Malm, U., Midha, K.K., 1990. Defining treatment refractoriness in schizophrenia. *Schizophr Bull* 16(4), 551-561.
- Cardwell, B.A., Nakai, B., 1995. Seizure activity in combined clozapine and ECT: a retrospective view. *Convuls Ther* 11(2), 110-113.
- Charlson, F., Siskind, D., Doi, S.A.R., McCallum, E., Broome, A., Lie, D.C., 2012. ECT efficacy and treatment course: A systematic review and meta-analysis of twice vs thrice weekly schedules. *Journal of affective disorders* 138(1–2), 1-8.
- Cipriani, A., Boso, M., Barbui, C., 2009. Clozapine combined with different antipsychotic drugs for treatment resistant schizophrenia. *Cochrane Database Syst Rev* 8(3).
- Conley, R.R., Buchanan, R.W., 1997. Evaluation of treatment-resistant schizophrenia. *Schizophr Bull* 23(4), 663-674.
- Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. *Bmj* 315(7109), 629-634.
- Flamarique, I., Castro-Fornieles, J., Garrido, J.M., de la Serna, E., Pons, A., Bernardo, M., Baeza, I., 2012. Electroconvulsive therapy and clozapine in adolescents with schizophrenia spectrum disorders: is it a safe and effective combination? *J Clin Psychopharmacol* 32(6), 756-766.
- Frankenburg, F.R., Suppes, T., McLean, P.E., 1993. Combined Clozapine and Electroconvulsive Therapy. *The Journal of ECT* 9(3), 176-180.

Garg R, Chavan Bir S, Arun P, 2012. Short-Term Efficacy of Electroconvulsive Therapy in Treatment-Resistant Schizophrenia. *German Journal of Psychiatry* 15, 44-49.

Garg, R., Chavan, B.S., Arun, P., 2011. Quality of life after electroconvulsive therapy in persons with treatment resistant schizophrenia. *The Indian journal of medical research* 133, 641-644.

Gazdag, G., Kocsis-Ficzere, N., Tolna, J., 2006. The augmentation of clozapine treatment with electroconvulsive therapy. *Ideggyogy Sz* 59(7-8), 261-267.

Gerretsen, P., Diaz, P., Mamo, D., Kavanagh, D., Menon, M., Pollock, B.G., Graff-Guerrero, A., 2011. Transient insight induction with electroconvulsive therapy in a patient with refractory schizophrenia: a case report and systematic literature review. *J Ect* 27(3), 247-250.

Grover, S., Hazari, N., Chakrabarti, S., Avasthi, A., 2015. Augmentation of Clozapine With ECT: Observations From India. *Am J Psychiatry* 172(5), 487.

Havaki-Kontaxaki, B.J., Ferentinos, P.P., Kontaxakis, V.P., Paplos, K.G., Soldatos, C.R., 2006. Concurrent administration of clozapine and electroconvulsive therapy in clozapine-resistant schizophrenia. *Clin Neuropharmacol* 29(1), 52-56.

Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. *Bmj* 327(7414), 557-560.

Husni M, H.J., Peat C., 1999. Clozapine does not increase ECT-seizure duration. *Can J Psychiatry* 44, 190-191.

Hustig, H., Onilov, R., 2009. ECT rekindles pharmacological response in schizophrenia. *Eur Psychiatry* 24(8), 521-525.

Kales, H.C., Dequardo, J.R., Tandon, R., 1999. Combined electroconvulsive therapy and clozapine in treatment-resistant schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 23(3), 547-556.

Keller, S., Drexler, H., Lichtenberg, P., 2009. Very high-dose clozapine and electroconvulsive therapy combination treatment in a patient with schizophrenia. *J ECT* 25(4), 280-281.

Kennedy, J.L., Altar, C.A., Taylor, D.L., Degtiar, I., Hornberger, J.C., 2014. The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. *International clinical psychopharmacology* 29(2), 63-76.

Kho, K.H., Blansjaar, B.A., de Vries, S., Babuskova, D., Zwinderman, A.H., Linszen, D.H., 2004. Electroconvulsive therapy for the treatment of clozapine nonresponders suffering from schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience* 254(6), 372-379.

Klapheke, M.M., 1991. Clozapine, ECT, and Schizoaffective Disorder, Bipolar Type. *Convuls Ther* 7(1), 36-39.

Kristensen, D., Bauer, J., Hageman, I., Jorgensen, M.B., 2011. Electroconvulsive therapy for treating schizophrenia: a chart review of patients from two catchment areas. *Eur Arch Psychiatry Clin Neurosci* 261(6), 425-432.

Kupchik, M., Spivak, B., Mester, R., Reznik, I., Gonen, N., Weizman, A., Kotler, M., 2000. Combined electroconvulsive-clozapine therapy. *Clin Neuropharmacol* 23(1), 14-16.

Kurian, S., Tharyan, P., Jacob, K.S., 2005. Combination of ECT and clozapine in drug-resistant schizophrenia. *Indian J Psychiatry* 47(4), 0019-5545.

Kursawe, H.K., Schmikaly, R., 1988. [Fatal pulmonary embolism following mitigated electroconvulsive therapy. A case report from the intensive care viewpoint]. *Psychiatr Neurol Med Psychol Beih* 40, 107-108.

Lee, W.K., Shiah, I.S., Chen, C.Y., Lin, T.L., Shen, L.J., 2008. Electroconvulsive therapy-associated Pisa syndrome in clozapine treatment. *Psychiatry and clinical neurosciences* 62(6), 753.

Manjunatha, N., Ram Kumar, G.S., Vidyendaran, R., Muralidharan, K., John, J.P., 2011. Delayed onset, protracted delirium and aspiration pneumonitis associated with a combination of clozapine and electroconvulsive therapy. *Indian journal of psychological medicine* 33(1), 80-82.

Masoudzadeh, A., Khalilian, A.R., 2007. Comparative study of clozapine, electroshock and the combination of ECT with clozapine in treatment-resistant schizophrenic patients. *Pakistan journal of biological sciences: PJBS* 10(23), 4287-4290.

Meltzer, H.Y., 1992. Treatment of the neuroleptic-nonresponsive schizophrenic patient. *Schizophr Bull* 18(3), 515-542.

Meltzer, H.Y., 1997. Treatment-resistant schizophrenia--the role of clozapine. *Current medical research and opinion* 14(1), 1-20.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 151(4), 264-269.

NICE, 2014. Psychosis and schizophrenia in adults: treatment and management (Clinical guideline 178). Royal College of Psychiatrists, London.

Pawełczyk, T., Kołodziej-Kowalska, E., Pawełczyk, A., Rabe-Jabłońska, J., 2014. Effectiveness and clinical predictors of response to combined ECT and antipsychotic therapy in patients with treatment-resistant schizophrenia and dominant negative symptoms. *Psychiatry Research* 220(1-2), 175-180.

Petrides, G., Malur, C., Braga, R.J., Bailine, S.H., Schooler, N.R., Malhotra, A.K., Kane, J.M., Sanghani, S., Goldberg, T.E., John, M., Mendelowitz, A., 2014. Electroconvulsive Therapy Augmentation in Clozapine-Resistant Schizophrenia: A Prospective, Randomized Study. *Am J Psychiatry* 171(10), 1306-1313.

Petrides, G., Malur, C., Braga, R.J., Bailine, S.H., Schooler, N.R., Malhotra, A.K., Kane, J.M., Sanghani, S., Goldberg, T.E., John, M., Mendelowitz, A., 2015. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. *Am J Psychiatry* 172(1), 52-58.

Porcelli, S., Balzarro, B., Serretti, A., 2012. Clozapine resistance: augmentation strategies. *Eur Neuropsychopharmacol* 22(3), 165-182.

Remington, G., Saha, A., Chong, S.A., Shammi, C., 2005. Augmentation strategies in clozapine-resistant schizophrenia. *CNS Drugs* 19(10), 843-872.

Rose, D., Fleischmann, P., Wykes, T., Leese, M., Bindman, J., 2003. Patients' perspectives on electroconvulsive therapy: systematic review. *Bmj* 326(7403).

Rose, D.S., Wykes, T.H., Bindman, J.P., Fleischmann, P.S., 2005. Information, consent and perceived coercion: patients' perspectives on electroconvulsive therapy. *Br J Psychiatry* 186, 54-59.

Safferman, A.Z., Munne, R., 1992. Combining Clozapine with ECT. *Convs Ther* 8(2), 141-143.

Saha, S., Chant, D., Welham, J., McGrath, J., 2005. A systematic review of the prevalence of schizophrenia. *PLoS medicine* 2(5), e141.

Sienaert, P., Bouckaert, F., Fernandez, I., Hagon, A., Hagon, B., Peuskens, J., 2004. Propofol in the management of postictal delirium with clozapine-electroconvulsive therapy combination. *J Ect* 20(4), 254-257.

Sinha, D., Shah, H.R., 2013. Fatal pulmonary embolism in a patient treated with clozapine and electroconvulsive therapy. *IJMPS* 4(4), 09-11.

Taylor, D.M., Smith, L., Gee, S.H., Nielsen, J., 2012. Augmentation of clozapine with a second antipsychotic - a meta-analysis. *Acta Psychiatr Scand* 125(1), 15-24.

Tharyan, P., Adams, C.E., 2005. Electroconvulsive therapy for schizophrenia. *Cochrane Database Syst Rev* 18(2).

Tranulis, C., Mouaffak, F., Chouchana, L., Stip, E., Gourevitch, R., Poirier, M.F., Olie, J.P., Loo, H., Gourion, D., 2006. Somatic augmentation strategies in clozapine resistance--what facts? *Clin Neuropharmacol* 29(1), 34-44.

Vowels, E.C., Hittur Lingappa, S., Bastiampillai, T., 2014. Combination clozapine and electroconvulsive therapy in a patient with schizophrenia and comorbid intellectual disability. *The Australian and New Zealand journal of psychiatry* 48(7), 689-690.

Waite, J., Easton, A., 2013. The ECT Handbook (3rd edition): The Royal College of Psychiatrists' Special Committee on ECT. Royal College of Psychiatrists, London.

Yoshino, Y., Ozaki, Y., Kawasoe, K., Ochi, S., Niiya, T., Sonobe, N., Matsumoto, T., Ueno, S., 2014. Combined clozapine and electroconvulsive therapy in a Japanese schizophrenia patient: a case report. *Clinical psychopharmacology and neuroscience : the official scientific journal of the Korean College of Neuropsychopharmacology* 12(2), 160-162.

Table1: Controlled trials , open label prospective studies and retrospective reviews of C+ECT

Study	Design	Cases	Mean clozapine dose (+/- mean serum clozapine level) during ECT	ECT treatment details (including mean no. of treatments, (SDs)	Response	Adverse events (AEs)	Follow-up
All studies		n=140	366.6mg (n=101) ; 477.3 mg/L	10.7 (n=140)	62% (n=55/89 cases)	7.1% (n=10/140)	40% relapsed (n=12/30)
Petrides et al. 2014	Single blind RCT Crossover trial design	39 with TRS ECT plus clozapine group=20; clozapine-only group n=19	518.2 mg/day Serum clozapine level 842.2ng/ml	15.6 B/L ECT treatments Twice weekly	Response defined as decrease of \geq 40% from baseline psychotic subscale score on BPRS . 50% (n=10/20) in C+ECT group responded -0% in the clozapine-only group Crossover sample: n=19 Crossover sample response : 47.4% (9/19) Overall response to C+ECT of 48.7% , (19/39)	No significant treatment related AEs. No significant difference in change in global neuro-cognition between baseline and end of ECT between groups. Speed of processing reduced in C+ECT group (greater decrease in Rey Auditory Verbal Learning Test score of 1.5 (0.5) in C+ECT group compared to clozapine-only group, p=0.0063)) within one week of ECT completion Transient confusion (n=2)	Not yet reported (personal communication)
Masoudzadeh et al. 2007	RCT (unblinded)	18 with TRS 6&6&6= 3 groups	Not reported	All groups: 12 U/L ECT treatments Three times weekly	C+ECT group: Significant improvement – Total PANSS reduction of 71% (99-29) in C+ECT group Significantly > greater than both	No serious AEs.	No follow-up

					<p>ECT only and clozapine only group</p> <p>ECT only-PANSS total reduction of 40% (99-60)</p> <p>& Clozapine only - PANSS total reduction of 46% (96-52) in (F=189.15, df=4.63, p<0.001)</p>		
Pawelczyk et al., 2014	Open label trial	8 with TRS	306.25mg/day	<p>15.75 B/L (2.38) ECT treatments</p> <p>Three times weekly</p>	<p>Response defined as decrease of \geq 25% in total PANSS :</p> <p>PANSS total 25% (n=2/8);</p> <p>PANSS positive 50% (n=4/8);</p> <p>PANSS negative 0% (0/8)</p> <p>Outcome:</p> <p>25% responded</p>	Prolonged seizures (\geq 90s) were observed in 3 patients (90, 100, and 200 secs)	No follow-up
Garg et al 2012	Open label trial	11 with TRS	331.8mg/day (100.7) Range: (150 – 500mg)	<p>6.7 B/L ECT treatments (range 6-10 ECT treatments)</p>	<p>Response defined as decrease of \geq 30% in BPRS :</p> <p>72.7% (8/11) responded</p> <p>BPRS scores:</p> <p>pre ECT- 55.9 (7.2) decrease to Post ECT-37.5 (16.3) (p=0.005)</p> <p>PANSS scores significantly improved:</p> <p>Pre ECT- Total PANSS mean score- 89.3 (18.5) decreased to mean score 67.7 (25.5) (p=0.008);</p>	No serious AEs.	No follow-up

Hustig and Onilov, 2009	Open label trial	2 with TRS	Not reported	16 B/L ECT treatments	ECT improved CGI scores: CGI decreased from 6-4 100% response rate	None reported	Clinical improvement maintained at 12 months. 0/2 relapsed
Kho et al. 2004	Open label trial	11 with TRS	454.5mg/day (range 250mg-800mg/day) Serum clozapine level 440 ng/ml	8.1 ECT treatments twice weekly U/L for n=10 and B/L for n=3	Response defined as decrease of $\geq 30\%$ in baseline Total PANSS: 72.7% (n=8/11) responded Mean improvement in total PANSS score of 21	Transient memory problems (n=2)	Mean follow up 14.6 weeks Range (3-42) 5/8 patients relapsed
Kristensen et al. 2011	Retrospective chart review	20 (TRS=15 and TR SA=5)	No dose reported	10 ECT treatments (range 2-24) BL and twice weekly	90% (18/20) showed an 'excellent or good response'* 13/15 for TRS and 5/5 for TR SA		7/20 cases required maintenance ECT
Gazdag et al. 2006	Retrospective chart review	43 with TRS (n=27) or TR SA (n=16)	250mg/day	4.7 ECT treatments Twice weekly and B/L	Mean change in CGI of 2.3. Greatest improvement in TR SA group (n=16): CGI decreased from 6.25 pre-ECT to 2.31 post-ECT.		No follow-up

Table 2. Update from previous systematic reviews C+ECT

	Kupchik, 2000	Havaki-Kontaxaki, 2006	Lally, 2015 (Current review)	
Included RCTs	0	0	2	

Included open label trials and retrospective reviews	0	1	6	
Included case series and case reports	3 and 11		6 and 15	
Sample size	35 (17 with ECT added to clozapine)	22	192	
Response to C+ECT	67%	73%	76%	
Mean number ECT treatments	12	11.5	11.3	
Adverse events	17%	23%	14%	
Follow up data:				
Sample size	None reported or	22	62	
Relapse rate	found	55%	32%	

Supplementary table 1. Case series of clozapine augmented with ECT in TRS							
Study	No. cases	Mean age and duration of illness (DOI)	Mean Clozapine dose during ECT (and serum clozapine levels if provided)	ECT treatment Details (including mean no. of treatments and stimulus and seizure duration)	Outcome and measures used	Adverse Events	Maintenance Treatment Follow-up
All cases:	37	Mean age: 32.9 years/ DOI:15.4 years		13.3	74% (n=20/27) with significant reduction in BPRS or PANSS scores	10.8% (4/37) of cases with adverse events reported	20% (n=4/20) relapsed. Range of follow up 1-108 months
Grover et al. 2015	11	Mean age: 32.7 years / DOI:10.3 years		12.8 (range 6-30) BL Mean seizure duration: 39.9 seconds	100 % (11/11 (as communicated by author) with significant reduction in PANSS total scores (>20%) Mean reduction PANSS total =23.2	2 with 'prolonged' seizure (duration not stated); 2 with brief (approximately 2 hours) post ictal confusion	No relapse , 0/11 Duration of follow-up: 6 moths-108 month
Kurian at al. 2005	3 with TRS	Mean age: 26 years/		8-10 ECT treatments	All with a 40-50% reduction in BPRS scores	None.	No follow-up reported
Kales et al. 1999	5 with TRS	Mean age: 49.1 years Mean DOI: 29.4 years	540mg/day (200-900mg/day)	12.2 ECT treatments (range 5-12) BL	PANSS (n=2) Mean improvement of 48.5 (123.5-75) CGI (n=5) Mean improvement 1.8 (6-4); Mean GAF improvement: 22 (range-15-55)	None	3/5 relapsed. Duration of follow-up 4-104 weeks One required additional ECT courses due to relapse within 1 month of discontinuation
Benatov et al. 1996	4 with TRS	Age N/A Mean DOI: 18.25 years		14.25 ECT treatments	BPRS (n=3) One patient 'completely recovered' Decrease in BPRS scores >50% in another. Other two BPRS	None	¾ no relapse reported at follow up; duration of 6 to 24 months of follow -up Maintenance dose of clozapine average 400mg

					<p>scores decrease from 71.5 to 42;</p> <p>>40% improvement in BPRS in 3 cases; modest effect in other case</p>		/day
Cardwell et al. 1995	5 (PS=4; SA=3)	Mean age: 41.25 years		21.6 ECT treatments (17-31)	<p>26.9% improvement in total BPRS;</p> <p>25.3% improvement in positive BPRS scores;</p> <p>21.3% improvement in negative BPRS scores;</p>	None	No follow-up reported
Frankenburg et al. 1993	9 (n=2 Schiz; n=7 SA)	<p>Mean Age: 36.3years</p> <p>Mean DOI: 14.6 years</p>	75-550mg/day	<p>11 ECT treatments</p> <p>Seizure duration: 54.2 seconds</p>	<p>3 Pts:</p> <p>marked/moderate response =3;</p> <p>minimal response =3</p> <p>minimal/</p> <p>no response=3</p>	None	No follow-up reported

Supplementary table 2. Case reports of clozapine augmented with ECT in TRS

Case	Patient age and gender	Diagnosis as reported and duration of illness	Clozapine dose when ECT commenced (and serum levels if provided)	Psychotropic medication during ECT (and serum levels if provided)	ECT treatment Details (including mean stimulus if provided)	Outcome and measures used	Adverse Events	Maintenance Treatment Follow-up
All cases (n=15)	31.5 years	14 with TRS and 1 with TR SAD		Mean dose: 626.7mg	11.6 (14/15 with BL ECT)	80% responded to C+ECT (n=8/10)	Adverse effects were reported in 11/15. n=4 :mild and transient n=4: adverse effects led to discontinuation of ECT. N=1:death secondary to PE	44%(n=4/9) relapsed 33% (n=4/12) maintenance ECT for longer than 1 month
Bannour et al (2014)	32, Female	Undifferentiated Schizophrenia , 11 years	700mg bd	Clozapine 700mg bd	16 sessions of BL ECT (3 sessions per week)	BPRS score decreased from 95 to 29	None reported	ECT Continued at the rate of 1 session per

								<p>month.</p> <p>After 24 sessions, patient was 'well stabilized', and functioning socially</p>
<p>Bhatia et al (1998)</p>	<p>35, Male</p>	<p>Paranoid Schizophrenia , 4 years</p>	<p>850mg daily</p>	<p>Pimozide (during ECT course 1 and 2)</p> <p>Clozapine (during ECT course 3, titrated during treatment to 800mg)</p> <p>Clonazepam 0.5mg tds</p>	<p>3 courses of bilateral ECT during 60-week hospital stay: 13, 10 and 9 sessions</p>	<p>BPRS from 69 on admission to 37 on discharge</p>	<p>Seizure at 20 months, unrelated to ECT, changed to Olanzapine</p>	<p>No further ECT</p> <p>Discharged to community</p> <p>Stable at 20 months</p>
<p>Biederman et al (2011)</p>	<p>39, Male</p>	<p>Paranoid Schizophrenia , over 20 years</p>	<p>300mg daily (previously up to 800mg)</p>	<p>Clozapine 300mg daily</p>	<p>12 right unilateral ECT sessions</p>	<p>PANSS total decreased from 78 at baseline to 67 one month post ECT</p> <p>Slight cognitive improvements were measured,</p>	<p>None reported</p>	<p>Not reported</p>

						and these continued at least 1 month after ECT		
Gerretsen et al (2011)	39, Male	'Refractory schizophrenia with a strong affective component'	450mg bd; 743 ng/mL; (previous augmentation with Valproate d/c on starting ECT)	Clozapine 450mg bd	15 bilateral ECT treatments Specifications: pulse width, 1.0; frequency, 60 Hz; duration, 6.0 seconds; charge, 576 mC; seizure duration, 27-59 seconds)	BPRS: 3 months before ECT = 64; during ECT 26	Cognitive dysfunction on days of treatment (MMSE improved from 27/30 to 29/30 between ECT and MoCA improved from 22/30 to 25/30 between treatments) Abnormal EEG after 15 treatments- suggestive of encephelopathic clinical picture	Maintained on clozapine and reduced to twice weekly bilateral ECT for 3 weeks. Delusional preoccupations intensified between treatments (BPRS = 42) ECT discontinued owing to the risk of cognitive deficits with prolonged treatment.
Keller et al (2009)	19, Male	Paranoid Schizophrenia, 6 years	1600 mg daily; 917 ng/mL (previously up to 1800mg daily)	Increased to 1700mg during treatment; 1083ng/mL	8 weeks bilateral ECT (3/week for 4 weeks, 2/week for 4 weeks)	BPRS From 34 pre-treatment to 30 post-treatment	Postictal confusion and mild difficulties with anterograde memory	1 per week for 4 weeks

Klapeheke et al (1991)	26, Female	Schizoaffective Disorder, Bipolar type (duration not reported)	450mg daily	Titrated during ECT to 600mg daily	9 sessions bilateral, brief pulse ECT- 14 adequate seizures (Pulse freq 50/0Hz Pulse width 0.75 or 1.5ms Duration 1.25 or 1.5s)	'Dramatic clinical response with resolution of hallucinations, delusions and thought disorder	Tachycardia only	Sustained improvement over 3 weeks with continued upward titration of Clozapine (to 400mg bd)
Lee WK et al (2008)	57, Female	Schizophrenia , 30 years	400mg daily	Clozapine 400mg daily	10 sessions bilateral ECT, then discontinued due to a/e*	-	*PISA SYNDROME	Clozapine reduced to 25mg due to s/e, then maintained at 300mg after
Manjunatha et al (2011) CASE 1	39, Male	Paranoid Schizophrenia , (duration not reported)	400mg daily	Clozapine 400mg daily	Bitemporal, thrice-weekly, suprathreshold, modified ECT Stopped after 12 th session due to a/e*	-	*DELIRIUM	Complete recovery from delirium within 48 h without any further complications; Clozapine was restarted after 2 days; dose gradually increased to 150 mg
Manjunatha et al (2011) CASE 2	40, Male	Paranoid Schizophrenia , (duration not reported)	300mg daily	Clozapine 300mg daily	Bitemporal, thrice-weekly, suprathreshold, modified ECT Stopped after 6 th session due to a/e*	-	*DELIRIUM and ASPIRATION PNEUMONITIS	Following recovery, Clozapine monotherapy was restarted at a dose of 300 mg/day without re-emergence of delirium

Safferman et al (1992)	33, Female	Paranoid Schizophrenia , 10 years	400mg daily	Clozapine 400mg daily, Lorazepam tapered and stopped after 3 rd ECT	8 bilateral ECT sessions (pulse freq 60-80hz, pulse width 1.4-1.6ms, stimulus duration 1.4-1.6s)	Positive symptoms 'markedly reduced in intensity', improved sociality	Mild hypertension and tachycardia	Clozapine increased to 450mg; after 3 weeks discharged
Sieneart et al (2004)	37, Male	Paranoid Schizophrenia (duration not reported)	600mg daily	Clozapine 600mg daily Reduced to 450mg daily after 3 rd treatment due to a/e*	Bilateral ECT, 11 treatments (Pulse width 0.5 milliseconds, frequency 30 Hz, duration 5 seconds, charge 120 mC, current 800 mA)	Hours and days after 1 st treatment: 'remarkable diminishment of anxiety, hostility, and agitation' CDSS 6 at baseline, 1 after the 11th treatment. PECC 80 before the start of treatment, 38 after the 11th treatment.	Motor agitation and confusion directly after 1 st treatment *Severe delirium after 3 rd treatment Further episodes of delirium following further treatments	Maintenance-ECT on a once a-week schedule No further data on outcome reported
Sinha et al, 2013	22, Male	Paranoid Schizophrenia (duration not reported)	100mg daily	Clozapine 100mg daily	4 ECT treatments	-	Patient died from pulmonary embolism after 4 th treatment	-

Vowels et al (2014)	Female , 18	Schizophrenia and Moderate Intellectual Disability, (duration not reported)	500mg daily	Clozapine 500mg daily	1 st Treatment: 8 ECT sessions 2 nd Treatment: 12 ECT sessions	1 st Treatment: significant improvement was observed with no evidence of ongoing auditory hallucinations or physical aggression. 2 nd Treatment: 'again result[ed] in improvement' Relapse after 1-2 weeks after both treatments	None reported	'With continuation ECT (currently at a total of more than 35 sessions), continues to show behavioural stability, is able to attend school, and has been discharged to supported community accommodation following a 16 month admission'
Yoshino et al (2014)	Female , 37	Schizophrenia , 11 years	500mg daily	Clozapine 500mg	Bilateral ECT- 10 treatments (2 or 3 per week)	BPRS Before Clozapine: 81; on Clozapine: reduced to 67; after one course of ECT reduced to 40	Anterograde amnesia-resolved after a few hours	Continuation (maintenance) ECT was then done twice every 4 weeks and there were no significant ill effects. Maintenance ECT

